

## RISK FACTORS FOR ADENOCARCINOMA OF THE LUNG

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The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979-1982 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio (OR) = 4.49) and females (OR = 3.95) and were found to increase significantly ( $p < 0.01$ ) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ( $p = 0.05$ ). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval (CI) = 0.39-2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% CI = 0.97-5.12). The results suggest the need to develop cell type-specific etiologic hypotheses.

air pollution; lung neoplasms; tobacco smoke pollution

Recent evidence indicates that lung cancer may encompass several morphologically and clinically distinct diseases (1, 2). In industrialized western nations, incidence rates are highest for squamous cell carcinoma, followed by adenocarcinoma (3, 4).

The relation between squamous cell and small cell carcinomas and cigarette smoking

is well-established, but the relation between adenocarcinoma and cigarette smoking is less clear (3, 5, 6).

Adenocarcinoma is the most frequently diagnosed form of lung cancer in the United States among women and nonsmokers (3, 7). In a series of nearly 30,000 cases of primary lung cancer, 22 per cent were spec-

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ified as adenocarcinoma among males compared with 37 per cent among females (8). The role of occupational exposures in the etiology of adenocarcinoma remains inconclusive (9, 10). Recently, a disproportionate increase in the incidence of adenocarcinoma has been noted in the United States (5). The changing histologic patterns of lung cancer incidence may be due to a change in diagnostic practices and classification or to increasing exposure to environmental carcinogens.

The present investigation was designed to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. A case-control study was conducted to provide additional data concerning the relation between exposure variables and this infrequently studied and poorly understood form of lung cancer.

#### MATERIALS AND METHODS

Cases and controls were identified through the population-based Colorado Central Cancer Registry maintained by the Colorado Department of Health. For the years and counties included, reporting was essentially complete. All diagnoses were microscopically confirmed and classified according to histologic type. Study participants were required to have resided in the Denver metropolitan area for at least six months prior to cancer diagnosis in order to reduce migration bias.

##### *Case selection*

A total of 149 eligible cases of adenocarcinoma (*International Classification of Diseases* (ICD) code 163) were identified in the five-county Denver metropolitan area from 1979-1982. Selection was restricted to white males and white females. These adenocarcinoma cases were stratified by age and sex. Of the 149 eligible cases, 31 could not be located, 15 refused to be interviewed, and one did not qualify. A total of 102 case interviews (50 males and 52 females) were completed. The mean ages for male and

female cases were 64.9 and 66.3 years, respectively.

##### *Control selection*

Controls were chosen from persons in the Colorado Central Cancer Registry who had cancer of sites considered to be unrelated to cigarette smoking. Specifically, persons with cancers of the colon (ICD code 153) and bone marrow (ICD code 169) diagnosed from 1979-1982 were chosen as controls and group-matched to adenocarcinoma cases according to age and sex. Matching was done at the group level so that the maximum number of cases and controls could be used in the analyses. Only whites were included in the study, and at least one control was required for each case within each age and sex stratum.

A total of 169 eligible controls were identified. Of these, 24 could not be located, 13 refused to be interviewed, and one did not qualify. A total of 131 usable interviews (65 males and 66 females) were completed. Among controls, 80 were colon cancer patients, and 51 were diagnosed with leukemia. The mean ages for male and female controls were 65.2 and 68.2 years, respectively.

##### *Data collection and analyses*

Epidemiologic data were collected by personal interview. The interviewer was unaware of whether the patient was a case or a control. A higher percentage of the interviews in the case group (68.6 per cent) than in the control group (38.9 per cent) were completed by a relative or a friend. Among the 70 nonsurviving cases, 56 interviews were completed with a spouse, seven interviews with a child, six with a sibling, and one with a close friend. For the 51 deceased controls, information was obtained from 42 spouses, six children, two siblings, and one close friend.

Socioeconomic status was assessed by examining two variables, education and income. Educational level was characterized by the highest grade of formal education completed. Gross income was ascertained

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for the previous year, or in case of retirees, for the year prior to retirement.

Smoking history was characterized for cigarettes, cigars, or pipefuls in terms of pack-years of exposure. Passive smoking data were analyzed as a dichotomous variable based on the smoking status of the patient's spouse and as a stratified variable based on the hours per day that the subject was in the presence of persons who were smoking.

Occupational data were analyzed according to industrial category, occupational category, and a self-assessment of the exposure of the respondent to known lung carcinogens in the workplace. Those industries and occupations known to be associated with an elevated risk for lung cancer were coded and multiplied by the number of years in each category to estimate exposure over time (11-13). In addition, each subject was shown a list of 12 groups of materials known to be lung carcinogens and was asked whether he or she had been exposed to the substances during a particular occupation. Pulmonary carcinogens included materials such as asbestos, chromium, nickel, uranium ore, and mustard gas. Positive responses were coded as integers and summed.

An index of exposure to community air pollution was developed based on estimated levels of total suspended particulates per census tract and the years of residence in each census tract (14). Total suspended particulate air pollution, which contains a benzene soluble fraction, was used as an indicator of polycyclic hydrocarbon (e.g., benzo[a]pyrene) levels. The total suspended particulate data were stratified into 10 air pollution exposure subgroups, and each census tract within the Denver area was assigned to a subgroup. The residence code consisted of years at each residence multiplied by the corresponding total suspended particulate exposure subgroup.

In the first set of analyses, stratified contingency tables were constructed to adjust for age and smoking for the primary risk factors (15-17). Odds ratios for each level

of exposure were calculated by Miettinen's standardized rate technique which controls for confounding factors (18). All analyses included adjustment for age based on the categories 30-49, 50-59, 60-69, 70-79, and 80-99 years. An extension of the Mantel-Haenszel procedure was used to statistically evaluate overall trends in the proportion of cases according to level of exposure to risk factors (19, 20).

Multiple logistic regression was used to obtain maximum likelihood point and interval estimates of the odds ratio, as well as to control for the effects of various confounding risk factors (21-23). The most significant predictors, based on the Mantel-Haenszel results, were included in the logistic model. The dependent variable in these analyses was lung adenocarcinoma (case (coded as 1) or control (coded as 0)). Independent variables were entered in intervals, as recommended by Schlesselman (24). In order to identify the potential confounding effect of the induction period of cancer, the exposure of each case or control to ambient air pollutants and industrial carcinogens was analyzed in two ways: 1) the entire residence and work history of each person was included, and 2) only exposures that took place 10 or more years prior to the time of diagnosis were considered. The analyses were completed both for all subjects and for primary respondents only, to assess the validity of the surrogate interview data. A multiple logistic regression model was also constructed for non-smoking female cases and controls.

## RESULTS

For both males and females, the age-standardized odds ratio for adenocarcinoma was significantly increased with increasing levels of prior cigarette use (table 1). The age-adjusted odds ratio for prior cigarette use among males was 4.49 (95 per cent confidence interval (CI) = 1.44-13.98). Among females, the risk due to cigarette smoking was 3.95 (95 per cent CI = 1.76-8.80). For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at

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TABLE 1

Adjusted odds ratios (OR) and trend tests for adenocarcinoma of the lung according to level of cigarette use and passive smoke exposure, metropolitan Denver, CO, 1979-1982

Factor	Males			Females		
	No. of cases	No. of controls	OR*	No. of cases	No. of controls	OR
Prior cigarette use (pack-years)						
0	4	19	1.00	19	47	1.00
1-39	14	19	4.06	10	13	1.68
≥40	32	27	7.68	23	6	14.80
Trend (p value)			(<0.01)			(<0.01)
Passive smoke exposure (hours/day)						
0-3	16	28	1.00	29	53	1.00
4-7	19	24	1.76	11	8	3.06
≥8	15	13	2.68	12	5	2.33
Trend (p value)			(0.46)			(0.05)

\* Odds ratio for prior cigarette use adjusted for age; odds ratio for passive smoke exposure adjusted for age and smoking.

different levels of passive smoke exposure followed an overall trend, statistically significant at the 0.05 level. The age- and smoking-adjusted odds ratio for passive smoke exposure (using 0-3 hours per day as the reference level) was 1.01 (95 per cent CI = 0.42-2.41) among males. The corresponding risk for females was 2.42 (95 per cent CI = 0.94-6.22). Odds ratios for passive smoke exposure were also calculated on a yes/no basis for the regular smoking history of the patient's spouse. The adenocarcinoma risk from smoking by the spouse was not significant for males (odds ratio (OR) = 1.40, 95 per cent CI = 0.66-2.14) or females (OR = 1.54, 95 per cent CI = 0.72-2.35).

The odds ratios and their 95 per cent confidence intervals for education level, income, community air pollution exposure history, and occupational exposures are presented in table 2. The lowest level of each variable was used as the reference category. Both education and income showed inverse trends with adenocarcinoma risk. Among males, annual income approached statistical significance with an odds ratio of 0.47 (95 per cent CI = 0.19-1.19). No significant risks in the age- and smoking-adjusted odds ratios were shown

for males or females according to their air pollution exposure history. No difference was noted regardless of whether the entire residence history of the patient or only the residence history 10 or more years prior to cancer diagnosis was used in the analysis. Of the occupational variables (industrial category, occupational category, or self-reported exposure to lung carcinogens), only occupational exposures for males bordered on significance (OR = 2.23, 95 per cent CI = 0.97-5.12).

The multiple logistic regression risk estimates for income, occupation, pack-years of cigarette use, and passive smoke exposure are shown in table 3. For both sexes combined, annual income showed an inverse association with adenocarcinoma risk after adjustment for other risk factors (OR = 0.85, 95 per cent CI = 0.72-0.98). A positive association between pack-years of cigarette use and cancer risk was found for males, females, and both sexes combined. The largest risk for adenocarcinoma associated with passive smoking was shown for females at the exposure level of 4-7 hours per day (OR = 1.91, 95 per cent CI = 0.78-3.03). The first-order interaction of pack-years of smoking and passive smoking was examined and found to be nonsignificant.

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TABLE 2

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to education, income, air pollution residence history, and occupation, metropolitan Denver, CO, 1979-1982

Factor	Males			Females		
	n	OR*	95% CI	n	OR	95% CI
Education level (highest grade)						
0-8	25	1.00		17	1.00	
9-17	90	0.59	0.23-1.54	101	0.73	0.23-2.31
Annual income (thousands of dollars)*						
<\$15,000	25	1.00		37	1.00	
≥\$15,000	86	0.47	0.19-1.19	78	0.71	0.28-1.85
Residence history (exposure-years)‡						
0-99	26	1.00		31	1.00	
≥100	89	1.66	0.66-4.19	87	1.51	0.58-3.96
Occupation (exposure-years)§						
0	76	1.00		112	1.00	
≥1	39	2.23	0.97-5.12	6	0.59	0.09-3.51

\* Odds ratio adjusted for age and smoking.

† Missing values.

‡ The product of years at each residence and the corresponding total suspended particulate exposure subgroup.

§ Occupations at high risk for lung cancer multiplied by the number of years in each category.

TABLE 3

Multiple logistic regression odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to income, occupation, cigarette use, and passive smoke exposure, metropolitan Denver, CO, 1979-1982

Factor	All subjects			Males			Females		
	n	OR*	95% CI	n	OR	95% CI	n	OR	95% CI
Income	233	0.85	0.72-0.98	115	0.85	0.66-1.03	118	0.84	0.64-1.03
Occupation	233	1.00	0.96-1.04	115	1.00	0.97-1.04	118	0.94	0.51-1.37
Pack-years									
0	89	1.00		23	1.00		66	1.00	
1-39	56	2.62	1.82-3.41	33	3.74	2.37-5.12	23	1.93	0.88-2.99
≥40	88	5.81	5.01-6.61	59	5.42	4.13-6.71	29	9.58	8.31-10.86
Passive smoking (hours/day)									
0-3	126	1.00		44	1.00		82	1.00	
4-7	62	1.24	0.53-1.95	43	0.84	0.00-1.80	19	1.91	0.78-3.03
≥8	45	1.37	0.54-2.20	28	1.17	0.10-2.24	17	1.21	0.00-2.68

\* Odds ratio adjusted for age, potential confounding factors, and sex when appropriate.

Logistic regression was conducted by using only primary respondents. These results were similar to those found when all respondents were included. Active smoking was the only risk factor significant at the 0.05 level based on the analysis of primary respondents. The odds ratios for pack-years of smoking were consistently smaller for primary respondents, whereas those for passive smoke exposure were larger when primary respondents were analyzed.

The risk of adenocarcinoma due to passive smoke exposure was examined among female nonsmokers (table 4). Nineteen female nonsmoking cases were identified (36.5 per cent). Due to size limitations, passive smoking was divided into two categories: 0-3 and four or more hours per day. An odds ratio of 1.68 (95 per cent CI = 0.39-2.97) was computed for the larger exposure category after adjustment for age, income, and occupation.

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TABLE 4  
Multiple logistic regression odds ratios (OR) and 95% confidence intervals (CI) for adenocarcinoma of the lung according to income, occupation, and passive smoke exposure among female nonsmokers, metropolitan Denver, CO, 1979-1982

Factor	n	OR*	95% CI
Income	66	0.85	0.60-1.11
Occupation	66	0.004	
Passive smoking (hours/day)			
0-3	56	1.00	
≥4	10	1.68	0.39-2.97

\* Odds ratio adjusted for age and potential confounding factors.

### DISCUSSION

Numerous case-control studies of lung cancer have been conducted over the past 30 years. Few, however, have examined the data according to histologic type. There appears to be a general consensus that the various histologic types of lung cancer have a multifactorial etiology which includes cigarette smoking and occupational and other environmental factors.

Smoking is the major risk factor for most types of lung cancer. In the United States, it is estimated that cigarette smoking may contribute to at least 80 per cent of lung cancer in males and 40 per cent in females (25). Several reports have suggested that smoking may not be the major risk factor for adenocarcinoma in certain populations (26-28). Among white males, the age-standardized relative risk estimates for lung adenocarcinoma according to prior cigarette use have ranged from less than one at low levels of smoking to about six at high levels of smoking (3, 29). Risk estimates of adenocarcinoma from smoking for females are commonly lower and vary widely among racial groups; for example, the relative risk estimates range from about one in Chinese women to four in Japanese women, and five in Hawaiian women (26, 30). The risk of smoking and adenocarcinoma for white females is usually between one and three, although the risk of lung cancer by histologic type has been studied

less frequently among females than among males (10, 30-32).

The current study found significant risk estimates for adenocarcinoma associated with smoking of 4.49 for males and 3.95 for females. The age-standardized risk estimates at different levels of cigarette use showed significant trends ( $p < 0.01$ ) for males and females, indicating that a dose-response relation between smoking and adenocarcinoma was present. The risk estimates based on multiple logistic regression analyses for smoking were generally lower than the odds ratios calculated by the methods of Mantel and Haenszel (15) and Miettinen (17), since logistic regression allowed for adjustment for multiple factors. The risk estimates for smoking and adenocarcinoma found in this study and the presence of a dose-response relation were consistent with other studies (29, 31, 33).

The effect of involuntary inhalation of sidestream smoke (passive smoking) on lung cancer etiology is a controversial current public health issue (34). Hirayama (35) reported a significant relative risk for lung cancer of 2.08 among wives of heavy smokers. A study conducted among Greek women found relative risks of 2.4 and 3.4 for wives of light and heavy smokers, respectively (36). A case-control study in Louisiana identified an increased risk for lung cancer among nonsmokers married to heavy smokers and for subjects whose mothers smoked (37). Garfinkel et al. (38) found an increased lung cancer risk for women whose husbands smoked 20 or more cigarettes per day. A recent study in Los Angeles found a slight increase in risk of adenocarcinoma among nonsmoking women exposed to passive smoke (39). Several other studies have failed to link passive smoke exposure to an increased risk of lung cancer (40-42). Prior studies that have evaluated passive smoking and lung cancer have differed in the index of passive smoke exposure, cell type, and degree of histologic verification (34).

In the present study, indexes of passive smoke exposure were obtained in two ways:

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1) by ascertaining the regular smoking history of the spouse of each subject on a yes/no basis; and 2) by determining the average hours per day that the subject was exposed to smoking (at home and at work). No significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ( $p = 0.05$ ) after adjustment for age and cigarette smoking. However, after adjustment by logistic regression for age, income, occupation, and cigarette smoking, no significant adenocarcinoma risk for passive smoke exposure was found among females.

The relatively large proportion of non-smoking female cases (36.5 per cent) observed in this study suggested the importance of other risk factors in adenocarcinoma etiology. A previous study found 19.5 per cent nonsmokers among female adenocarcinoma cases (39). Our study demonstrated a slightly elevated risk among female nonsmokers due to passive smoke exposure, consistent with the findings of Wu et al. (39). Deficiencies in passive smoking data in recent studies include: 1) no commonly established index of side-stream smoke exposure; 2) a lack of data on other indoor air pollutants such as radon; 3) the existence of a probable differential in accuracy of obtaining passive smoke exposure histories between living and deceased subjects; 4) a lack of evidence of changes in the peripheral bronchial epithelium of nonsmokers exposed to side-stream smoke (40); and 5) insufficient numbers of non-smoking lung cancer cases available for analyses. Despite these limitations, the relation between passive smoking and lung cancer deserves further investigation.

Although pollutants in the air have long been suspected to contribute to the etiology of lung cancer, epidemiologic evaluation has been hampered by difficulties in defining and measuring air pollution and in eval-

uating the effects of confounding variables such as smoking, occupation, and population mobility (43). A census tract analysis of lung cancer data, total suspended particulate air pollution, and median household income was reported previously for the Denver area (14). Our previous work showed a significant direct relation between male lung cancer rates and total suspended particulate air pollution ( $p < 0.02$ ). However, for both males and females, median household income explained a larger percentage of the variation in lung cancer rates than did particulate air pollution.

The data on residence history of cases and controls were analyzed to determine if differences in total suspended particulate air pollution exposure may have accounted for a portion of the adenocarcinoma incidence. There were only slight differences between cases and controls in mean or median years of residence in metropolitan Denver. Residence history was defined in terms of exposure-years (years of exposure to high or low total suspended particulates) in order to define an index of exposure for each case and control. Although, in Denver, cases commonly experienced more exposure-years, no significant differences between cases and controls were detected for males or females. Our data failed to show the presence of a large air pollution effect.

Occupational exposures may be important risk factors for lung cancer (44-51). Prior studies of lung cancer have demonstrated an increased risk for exposure to substances such as asbestos, arsenic, nickel, radon daughters, diagnostic radiation, and fossil fuel combustion products (44). Inconsistent findings have been reported regarding the importance of occupational factors in adenocarcinoma incidence (9, 10). In this study, occupational risks for adenocarcinoma were examined in two ways: 1) an a priori listing of industries and occupations in which workers are at high risk for lung cancer was used to code the work history data from each case or control; and 2) each subject was asked if he or she was ever exposed to a list of known lung carcinogens

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in the workplace. The exposures (industrial, occupational, or pulmonary carcinogens) were cumulated over the lifetime of the subject, and the analysis was based on a classification of any or no previous exposure. Only high-risk occupational history showed a borderline significant risk for adenocarcinoma among males after adjustment for age and smoking history. The occupational risk was smaller after multiple adjustment for age, income, cigarette smoking, and passive smoking. The relations between workplace exposures and adenocarcinoma risk were unchanged regardless of whether the entire work history of the subject or only the work history 10 or more years prior to diagnosis was used.

A difference in risk for lung cancer by social class has been observed whether measured primarily by occupation, income, or education (3). Part of the socioeconomic differential in lung cancer risk is due to smoking habits (52). In this study, education level and gross income were used as socioeconomic indicators. Income level showed a stronger association with adenocarcinoma risk after controlling for age and smoking than did education. Since colon cancer is correlated with socioeconomic status (53), it is possible that the use of colon cancer patients as controls in this study magnified the observed inverse relation between adenocarcinoma and income level. No statistically significant inverse association was noted in adenocarcinoma risk with respect to education level, although risk estimates were commonly lower at higher educational levels.

The issue of dietary vitamin A and lung cancer risk was not addressed in this study. Evidence is accumulating that a deficiency in dietary vitamin A may result in a higher risk for lung cancer and that a higher intake of vitamin A and its provitamins has an apparent protective effect (28, 54-59). Diet may be less important in our study since recent data have suggested that the inverse relation between vitamin A intake and lung cancer is strong for squamous cell and small

cell carcinomas but not for adenocarcinoma (29, 58).

This study used a higher proportion of surrogate interviews for cases (68.6 per cent) than of surrogate interviews for controls (38.9 per cent). Several investigators have attempted to characterize the validity of information obtained from surrogate interviews (60-62). Pickle et al. (60) found that siblings were best able to describe events that occurred early in life, whereas spouses and offspring best recounted events during adult life. Other studies have found that bias may be introduced because of inaccurate work histories given by next of kin (61) and that spouses may provide accurate demographic information and a crude estimate of smoking, but details of employment history and diet may be of lower validity (62). To address this problem, we conducted separate analyses for all respondents and for primary respondents. The results were highly comparable and indicated that some conclusions based on all respondents may have been conservative since adenocarcinoma risk estimates for passive smoking were commonly higher among primary respondents.

In light of the changing histopathologic patterns of lung cancer, the findings of this and other recent studies suggest the need to consider the various lung cancer cell types as different diseases. Future research should emphasize accurate histologic typing and the development of cell type-specific etiologic hypotheses.

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## ERRATA

The *Journal* has been notified by Dr. Ross Brownson of some errors that went undetected by his co-authors and himself in the "Materials and Methods" section of their recent article, "Risk Factors for Adenocarcinoma of the Lung" (*Am J Epidemiol* 1987;125:25-34). The authors used the nomenclature of the *International Classification of Diseases for Oncology* (ICD-O). Due to a typing error in the manuscript, the topography code they cite for adenocarcinoma of the lung, 163, is incorrect. The correct ICD-O code, and the one they used in the study, is 162, including morphology codes 81403, 82303, 82503, 82603, and 85503. The code that the authors cite for colon cancer (153) is correct. For cancer of the bone marrow, the code more explicitly is 169.1 (in the article, it is given as 169). The authors hope these oversights have caused no confusion to readers.

The *Journal* regrets an error in the title of table 4 in the recently published article by Khoury et al. entitled "Inbreeding and Prereproductive Mortality in the Old Order Amish. II. Genealogic Epidemiology of Prereproductive Mortality" (*Am J Epidemiol* 1987;125:462-72). In technical editing, the title was incorrectly changed to read "Demographic relative risk (RR) factors..." As correctly worded, the title in full should read: "Demographic risk factors for prereproductive mortality (before age 20 years) (PRM) in the Old Order Amish genealogy by year of birth."

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